Statements under 37 C.F.R. §1.173(c)

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 have been cancelled without prejudice toward the continuation of prosecution in a continuing application. Added claims 5-177 and 178-218 have also been cancelled without prejudice. Claims 219-238 are the only claims now pending in the case.

Pursuant to 37 C.F.R. §1.173(c), the following is an explanation of the support in the disclosure of the patent for the changes made to the claims by the present amendment.

In applicant's amendment of August 15, 2012, claims 177 and 210-218 were cancelled. These claims were cancelled because a rejection thereof was affirmed by the Board of Patent Appeals and Interferences (now the Patent Trial and Appeal Board). It was thought that deleting these claims would expedite allowance of the remaining claims that were free of all rejections. However, as the examiner has seen fit to reject the claims that had previously been held to be free of all rejections, applicant has opted to resubmit previously appearing claims 177 and 210-218 so that all claims may be further examined.

The new claims submitted herewith correspond with the previously appearing claims according to the following chart:

New Claim Number	Old Claim Number
229	210
230	211
231	177
232	212
233	213
234	214
235	215
236	216
237	217
238	218

No change to the language of the old claims has been made other than to correct the dependencies to refer to the new claim numbers. As support for all of the disclosure of claims 177 and 210-218 has previously been established when each of those claims were submitted or amended, no repetition of such support should be necessary here.

REMARKS

Claims 219-238 presently appear in this case. No claims have been allowed. The official action of November 14, 2012, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that binds β-amyloid and either inhibits aggregation of β-amyloid, maintains the solubility of soluble β-amyloid, or disaggregates an aggregate of β-amyloid. When the antibody is one that inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid, it does so at least to the extent that monoclonal antibody AMY-33 does so. The genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that either recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid. The human monoclonal antibody must be one that is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid. The invention also relates to a method for making such a pharmaceutical

formulation by first selecting the monoclonal antibody and then genetically engineering it prior to incorporating it into a pharmaceutical formulation.

Copy of Claims in Conventional Amended Format

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

Although none of the present claims is being amended, so that the examiner can see all of the claims now present in the case, the following is a recitation of all of the pending claims, including the newly added claims, shown in the conventional format, with the conventional claim descriptors:

1-218 (Cancelled).

218 (Previously Presented). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid

and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

219 (Previously Presented). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

220 (Previously Presented). The therapeutic composition of claim 219, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is

obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

221 (Previously Presented). The therapeutic composition of claim 219 or 220, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

222 (Previously Presented). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

223 (Previously Presented). The therapeutic composition of claim 222, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds

beta-amyloid and disaggregates an aggregate of human β-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

224 (Previously Presented). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

225 (Previously Presented). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

226 (Previously Presented). The therapeutic composition of claim 225, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an

aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

227 (Previously Presented). The therapeutic composition of claim 225 or 226, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

228 (Previously Presented). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

229 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid; and

wherein said antibody or fragment is not conjugated with a detectable moiety.

230 (New). The therapeutic composition of claim 229, wherein said genetically-engineered antibody of (2)(a) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal

antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

231 (New). The therapeutic composition of claim 229 or 230, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

232 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid.

233 (New). The therapeutic composition of claim 232, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an

extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid.

234 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

235 (New). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

236 (New). The therapeutic composition of claim 235, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at

least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

237 (New). The therapeutic composition of claim 235 or 236, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

238 (New). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

Continuing Obligations

It is noted that the examiner has reminded applicant and applicant acknowledges the continuing obligation under 37 CFR 1.178(b) to timely apprise the Office of any prior or

concurrent proceeding in which patent no. 5,688,651 is or was involved, and the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information that is material to patentability of the claims under consideration in the reissue application.

The examiner is hereby apprised that a divisional reissue of patent no. 5,688,651, application no. 11/358,951, had rejections affirmed by the Board of Patent Appeals and Interferences (now the Patent Trial and Appeal Board). This appeal decision has been appealed to the Court of Appeals for the Federal Circuit, appeal no. 2012-1689. The result of this appeal may affect rejections of some of the present claims. The appeal is presently pending.

Supplemental Reissue Declaration

Applicant recognizes its obligation to file a supplemental reissue declaration stating that every error which was corrected in the reissue application not covered by a prior declaration submitted in the application arose without any deceptive intention on the part of the applicant. It is not believed that another supplemental reissue declaration need be filed as all of the present claims have been covered by prior declarations.

Written Description Rejection

Claims 219-228 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims encompass a genus of antibody molecules or the production of such antibody molecules which are allegedly claimed by desired functional properties. The examiner has referred applicants to the written description guidelines insofar as they refer to products claimed by their function and antibodies to a genus of proteins. The examiner states that the claimed subject matter is drawn to a broad structural class of molecules and the recitation of binding to β-amyloid and disaggregating an aggregate of β-amyloid represents functional characteristics. The examiner states that there is no structure/function correlation provided, for example, between the desired epitope and the sequence corresponding to the antigen-binding (hypervariable) region of the antibody. The examiner states that the indicated immunogen does not provide a structural limitation for the antibodies. The examiner states that, apart from a method step to select for antibodies displaying the particular desired functional characteristics, there is no indication of any specific structural properties required for making the claimed genetically-engineered antibodies. The examiner states that the specification does not provide any

examples of a species that falls within the claimed genus of antibody molecules. The examiner states that applicant has not described the structures of a representative number of species of the genus now claimed but rather has presented the public with an idea about how to perform an assay that might identify some agents that fall within the scope of the claim. The examiner considers the instant situation to be analogous to that of *Centocor Ortho Biotech, Inc. v. Abbott Laboratories,* 636 F.3d 1341, 1351 (Fed. Cir. 2011) and that in *Centocor*, the claims were drawn to antibodies in which the antigen of interest was known but there was no description in the specification or prior art of the specific properties required. This rejection is respectfully traversed.

The present claims are based on the paragraph appearing in the present specification at column 5, lines 23-30, which states:

> In addition, the anti-aggregation molecule is screened for its ability to dissolve already aggregated proteins. The aggregated proteins are mixed with the anti-aggregation molecules under physiological conditions. It is then determined if the mixture produces nonaggregated target molecules that are bioactive even in the presence of, and bound to, the presumptive anti-aggregation molecule.

The example in the Written Description Training Materials, Revision 1, March 25, 2008, that is most closely related to the present claims is Example 13, relating to

monoclonal antibodies against a specifically identified antigen. This example demonstrates that written description for an antibody can be established even without any example of a specific antibody. The example explicitly posits, at the end of the first paragraph on page 45, that "there is no working or detailed prophetic example of an antibody that binds to antigen X." Despite the examiner's statements that specific structural or physical properties are required, and that structure/function correlation is required, such as by sequence information, and that a recognizable structure for the claimed antibody is required, the Example 13 in the Training Materials makes clear that none of this is necessary in light of the level of skill and knowledge in the art of antibodies. Example 13 determines that the production of antibodies against a well-characterized antigen was conventional. The Example explicitly states that the specification did not describe an antibody in structural terms, nor did it provide a structural chemical formula. There was no correlation between the function of binding to antigen X and the structure of the claimed antibody. Despite all of this, the Example finds the claim in question to satisfy the written description requirement as persons of skill in the art do not consider knowledge of the amino acid sequence of the variable regions critical for purposes of

assessing possession of an antibody (Training Materials, page 46). In view of the fact that antibody technology was well-developed and mature, the Example holds that one of skill in the art would have recognized that the disclosure of the adequately described antigen X put the applicant in possession of antibodies which bind to antigen X. It should be noticed that these Training Materials were formally acknowledged and given judicial notice by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

The examiner's reference to Examples 10 and 14 of the same Training Materials, at the bottom of page 4 of the rejection, is misplaced. The present claims are not directed to a product claimed solely by function, nor are they directed to antibodies to a genus of proteins. The immunogen here is a single well-defined polypeptide with the specified sequence of Aβ1-28. This is a single sequence, not a genus. Example 13 is applicable, not Example 14. Example 10 is not applicable because the claims are antibody claims; thus, Example 13 is applicable, not Example 10. Example 10 relates to miscellaneous proteins. Antibodies are different for the reasons explained in Example 13 in view of the fact that the antibody technology is well-developed and mature.

Example 13 is applicable to the present claims and requires withdrawal of this rejection, regardless of whether AMY-33 exemplifies the feature of disaggregating β-amyloid. The present specification discloses how to raise antibodies against the specified region of β-amyloid. Accordingly, the entire genus of antibodies against this region of β-amyloid has been disclosed and is in possession of applicant. The Training Materials say that this disclosure satisfies the written description requirement, despite the lack of any example and the absence of information about structure/function relationship. This is because of the well-developed and mature nature of the antibody art.

As is evidenced by the above-quoted portion of the present specification (column 5, lines 22-30), the specification discloses that one may screen to identify the claimed antibodies and it discloses how to conduct such a screen. There is no enablement rejection. Thus, this is completely dissimilar to the fact situation in the *Rochester* case relied upon by the examiner. In that case, the applicant had no idea what kind of molecule would have the properties sought in the proposed screen.

Here, one of ordinary skill in the art reading the present specification would be able to identify such an antibody as the specification puts one in possession of the

entire genus of antibodies to Aβ1-28. Identifying those antibodies from that genus having the desired properties is merely part of the antibody screening process that is well known in the art and highly developed and mature. It is a routine matter to screen the antibodies raised against Aβ1-28 to find the ones having the specified property. The present specification states that some of these antibodies possess this property. The presumptively accurate statement that such antibodies exist within the genus, all of which applicant was in possession of, is sufficient to satisfy the written description requirement for this sub-genus. While it is true that one cannot predict whether any given antibody raised against the Aβ1-28 peptide will necessarily have the required properties, it is fully predictable that a certain percentage of all such antibodies will, and these can be simply and readily identified using the fully described assay.

See *In re Wands*, 858 F.2d 731, 737-738 (Fed. Cir. 1988), which states:

> Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.
>
> … Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete

> antibodies against the antigen of interest.
>
> … In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}. **The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.** [Emphasis added.]

While *Wands* is an enablement case, it still serves as valid evidence that the use of such screening to obtain desired monoclonal antibodies is part of the conventional, routine and well-developed and mature technology that one can rely on to establish that applicant was in possession of the claimed sub-genus of antibodies for use in the methods of the present invention.

The examiner relies on the *Centocor v. Abbott* case. However, *Centocor* is not analogous to the present case. *Centocor* involved a claim to a monoclonal antibody against TNF-α that is fully human. Thus, not only is the Fc region humanized, but the variable region is also a human sequence. 636 F.3d at 1347. The court found that the specification taught how to make humanized antibody with a humanized Fc region but did not teach how to get a humanized variable region. There was simply no disclosure of how to do that.

Thus, the *Centocor* case does not involve a situation where one can raise a library of antibodies, some of which will have the desired properties and can be isolated by a simple screen. The application involved in the *Centocor* decision did not teach any antibody that is fully human or how to make it. The court stated at 1352 (636 F.3d at 1352):

> [O]btaining a high affinity, neutralizing A2 specific antibody with a human variable region was not possible in 1994 using "conventional," "routine" "well developed and mature" technology.

The first paragraph of section D (636 F. 3d at 1353) is also instructive where the court states:

> In view of the lack of written description in the specification for fully human, A2 specific neutralizing, high affinity antibodies, Centocor's argument that an inventor need not physically make an invention to claim it misses the mark. Indeed we have repeatedly indicated that the written description requirement does not demand either examples or an actual reduction to practice. [*Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc).] What it does demand is that one of skill in the art can "visualize or recognize" the claimed antibodies based on the specification's disclosure …. In other words, the specification must demonstrate constructive possession and the '775 patents specification fails to do so…. Centocor's asserted claims to fully human antibodies "merely recite a description of the problem to be solved while claiming all solutions to it." The actual inventive work of producing a human variable region was left for subsequent inventors to complete.

By contrast, there is nothing in the present description of the presently claimed antibodies that precludes their production by the conventional, routine and well-developed and mature technology acknowledged in the Training Materials. The present specification demonstrates constructive possession because it discloses possession of the library of antibodies from which the disaggregating antibodies can be selected and it discloses that a simple screen may be used to identify the claimed antibodies. Thus, the actual inventive work of producing such an antibody was not left for subsequent inventors to complete but, instead, the specification demonstrates constructive possession. The means of obtaining the library of hybridomas and the simple screen for disaggregation ability can be considered to be conventional, routine, well-developed and mature technology.

Given the presumptively accurate statements in the present specification (see *In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971)), it is fully predictable that some of the antibodies will have the disaggregating property, even if there is no specific embodiment thereof in the specification. Note that prior cases, such as *Centocor,* repeatedly emphasize that no example is necessary (see the above quote from Section D).

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 229-238 comply with the written description requirement for the same reasons as discussed above. Moreover, the present specification has a specific example of an antibody that inhibits aggregation, as called for in these claims. As to the written description rejection of these claims that was affirmed by the Board in its decision of August 6, 2012, a substantially identical rejection in the divisional application 11/358,951 has been appealed to the Federal Circuit, which appeal is currently pending. If the rejection in the divisional is overturned by the Federal Circuit, the same rejection will have to be withdrawn in this case. Thus, if the rejection affirmed by the Board is repeated for claims 229-238, applicant will ask that a response thereto be held in abeyance until after the Federal Circuit makes a decision on substantially the same rejection in the divisional application.

35 USC 102 Rejection

Claims 219, 220, 225 and 226 have been rejected under 35 USC 102(a) as being anticipated by Walker. The examiner states that Walker teaches a pharmaceutical composition comprising the monoclonal antibody 10D5 or Fab

fragments thereof in sterile saline. The examiner considers this to anticipate the language of the present claims because the recitation of a "genetically engineered antibody [that] is obtained by genetically engineering the DNA encoding a monoclonal antibody" amounts to a product-by-process limitation and has not been accorded patentable weight. The examiner states that there is nothing structurally or functionally to distinguish the claimed antibody from the prior art monoclonal antibody taught by Walker. The examiner considers that the broadest reasonable interpretation of the above-quoted language would be anticipated by the monoclonal antibody of Walker because the amino acid sequence of that antibody is identical to one which can be obtained by genetically engineering the DNA encoding a monoclonal antibody. The examiner also states that the DNA in a hybridoma is considered recombinant as a result of the method of making the hybridoma. This rejection is respectfully traversed.

It is not understood why the PTO considers it necessary to recycle rejections that had been made and overcome earlier in the lengthy prosecution of this case. Claims were first rejected as being anticipated by Walker in the Official action of July 29, 2005. The examiner then took the exact same position as the examiner now takes at the very

end of the rejection, i.e., that the DNA in a hybridoma is considered recombinant as a result of the method of making the hybridoma. However, after applicant amended the claims to read "obtained by genetically engineering the DNA encoding a monoclonal antibody," the examiner was convinced that this would not read on a monoclonal antibody produced by hybridoma technology and, on March 23, 2009, this rejection was explicitly withdrawn.

Now, the examiner states that the exact same antibody as the antibody of Walker could be produced in bacteria, yeast or human CHO cells, for example, by genetically engineering the DNA of those cells to insert the DNA encoding the monoclonal antibody of Walker and the antibody recombinantly produced by such cells would be indistinguishable from the antibody of Walker. As the examiner considers the language "genetically engineered antibody that is obtained by genetically engineering the DNA encoding a monoclonal antibody" to be product-by-process language, she believes that it can be anticipated by an antibody of the same structure that was not made by that method. The examiner considers the antibody of Walker to be of the same structure that can be made by genetically engineering the DNA encoding a monoclonal antibody and hence the anticipation rejection.

Respectfully, this logic is flawed. The examiner is relying on a definition of "genetically engineering" which is much too broad. In the example that the examiner provides, the antibodies are recombinantly produced in non-hybridoma cells, such as bacteria, yeast or human cells, such as CHO cells. While the sequence of the DNA in the bacterial, yeast or CHO cells has been altered so as to insert the DNA encoding the antibody of Walker, the nucleotide sequence encoding the protein to be produced, which sequence is recombinantly inserted into the DNA of those cells, has not been altered in any way. Thus, while the recombinantly produced bacteria, yeast or CHO cells are genetically engineered and their DNA has been genetically engineered, the DNA encoding the produced protein has not been genetically engineered. Thus, the antibody that is produced by such recombinant cells, even if it is the same as the Walker antibody, is not an antibody whose DNA has been "genetically engineered" and thus does not satisfy the terms of the rejected claims.

The definition of "genetic engineering" in Juo, "Concise Dictionary of Biomedicine and Molecular Biology," Second Edition, CRC Press, Boca Raton, FL, page 493 (copy submitted herewith), reads:

> **Genetic Engineering** The in vitro manipulation of the DNA to generate new, desirable recombinant sequences, genes, or organisms.

The DNA encoding the antibody in the examiner's example has not been manipulated to generate new desirable recombinant sequences. The DNA of the production cells has new recombinant sequences, but not the DNA encoding the antibody. The present claims all require "genetically engineering the DNA encoding a monoclonal antibody …." In the examiner's hypothetical example, the DNA encoding a monoclonal antibody has not been genetically engineered. The production cells have been genetically engineered, but the present claims require genetic engineering of the DNA encoding the antibody, meaning that the DNA encoding the monoclonal antibody has been altered in some way. In the examiner's example, that DNA encoding the antibody has not been genetically engineered as it has not been manipulated to generate new desirable recombinant sequences.

Furthermore, the examiner's interpretation of "obtained by genetically engineering the DNA encoding a monoclonal antibody" does not fall within the parameters of the broadest reasonable interpretation of this language. It is well established that during examination of a patent, claim terms are to be accorded their "broadest reasonable interpretation consistent with the specification." The examiner's interpretation is unreasonable and is not consistent with the specification.

The present specification distinguishes monoclonal antibodies and genetically engineered monoclonal antibodies. See, for example, column 10, lines 1-5, of the present specification. A construction of "genetically engineered monoclonal antibodies" that does not distinguish them from monoclonal antibodies is unreasonable as it is not consistent with the specification. The definition in the present claims requires that the DNA be modified or altered in some way, such as, for example, to change it into a single-chain antibody or a humanized antibody. This language cannot be construed as encompassing simply taking that DNA and transcribing it back into a protein using recombinant technology because that DNA has not been modified or altered in any way in order to produce the genetically engineered antibody. Thus, an antibody produced by recombinant technology that has a sequence identical to that of the monoclonal antibody does not fall within the definition of "genetically engineered antibody" as that term is interpreted in the broadest reasonable manner consistent with the specification. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

New claims 229-238 are free of this rejection for at least the same reasons as discussed above for the remainder of the claims.

Conclusion

It is submitted that all of the claims now present in case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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Gene Redundancy The presence of multiple copies of a gene in a chromosome.

Gene Regulatory Protein Protein that regulates gene expression and binding of RNA polymerase to promoter.

Gene Reiteration The presence of multiple copies of a particular gene.

Gene Splicing 1. The enzymatic manipulations by which one DNA fragment is attached to another. 2. The process by which the introns are removed and exons joined during mRNA synthesis.

Gene Substitution The replacement of one allele by another allele of the same gene.

Gene Superfamily The evolutionarily related genes or gene products with divergent functions, e.g., immunoglobulin superfamily.

Gene Therapy The introduction of a functional gene or genes into a recipient to correct a genetic defect.

Genera Plural of genus.

General Acid-Base Catalysis A form of catalysis that depends on transfer of protons.

General Anaphylaxis An IgE-mediated allergic reaction characterized by itching, swelling, or edema and wheezing respiration due to release of vasoactive amines (e.g., histamine) from mast cells.

General Transduction A phage-mediated transfer of host DNA from a donor cell to a recipient cell.

Generation Time The length of the cell cycle or time period needed for a cell population to double its numbers.

Generic Pertaining to genus or a substance not protected by patent.

Generic Name A technical, unsystematic type of name used in describing a drug.

-genesis A suffix meaning 1. origin and 2. formation or production.

Genetic Burden See genetic load.

Genetic Code Referring to the nucleotide triplets on mRNA that specify different amino acids in the process of translation.

Genetic Code Dictionary Referring to the 64 nucleotide triplets or codons resulting from the combination of four ribonucleotides of adenine, guanine, cytosine, and uracil.

Genetic Complementation The gene products of two mutant genes that can combine to give rise to a wild phenotype.

Genetic Cross 1. Mating of two organisms to produce genetic recombinants. 2. The progeny that contains genotypes of two or more parents, e.g., simultaneous infection of a bacterial cell with several types of phages. 3. The progeny derived from mating.

Genetic Disease 1. A disease due to changes in the genetic material. 2. A disease that is inherited in a mendelian fashion.

Genetic Dissection The use of recombination and mutation to piece together the various components of a given biological function.

Genetic Drift Changes in genotype or gene frequencies from generation to generation in a population as a result of random processes.

Genetic Engineering The in vitro manipulation of DNA to generate new, desirable recombinant sequences, genes, or organisms.

Genetic Equilibrium The frequency of a gene remains constant from generation to generation.

Genetic Expression See gene expression.

Genetic Homeostasis The self-regulating capacity of populations to adopt to the changing environment.

Genetic Load The average number of recessive lethal genes carried in the heterozygous condition by an individual in a population (also known as genetic burden).

Genetic Mapping A depiction of the linear order of genes along a chromosome.

Genetic Marker A detectable and genetically controlled marker on a chromosome of an organism.

Genetic Mosaic An organism that contains cells of different genotypes.

Genetic Polymorphism The presence of two or more alleles at a gene locus over a succession of generations.

Genetic Profiling A technique for providing profiles of DNA fragments resulting from digestion with restriction enzymes.

Genetic Recombination The combining of two different DNA molecules to produce a third molecule that is different from either of the original two.

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